Potential Obesogen Identified

Fungicide Triflumizole Is Associated with Increased Adipogenesis in Mice

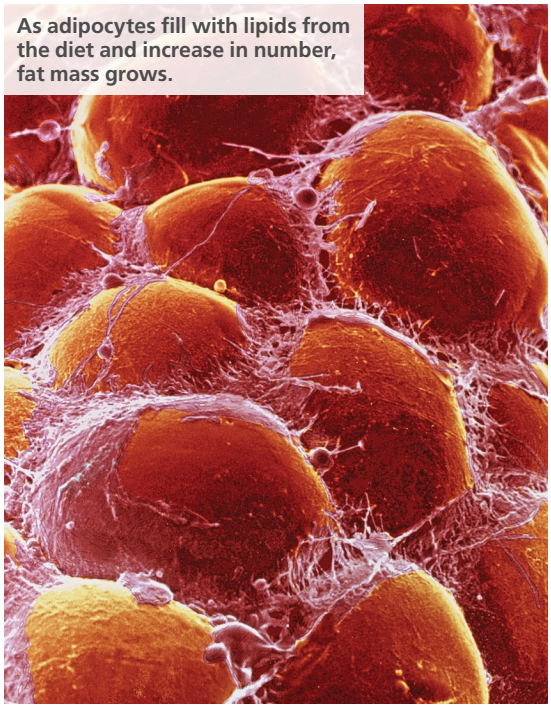
Obesogens are chemicals that increase either the number of fat cells in an organism or the amount of fat stored in those cells. Obesogens may also act indirectly on obesity by modulating appetite, satiety, or metabolism. Now researchers have identified a common agricultural chemical that appears to qualify as an obesogen because it nudges gene expression and stem cell differentiation toward becoming a fat cell [***EHP* 120(12):1720–1726; Li et al.**].

More than two-thirds of the U.S. population—twice the global average—is either overweight or obese. This is typically attributed to overeating and inactivity. But evidence that pets, laboratory animals, primates, and feral cats living in industrialized human societies also are showing a rise in obesity suggests that environmental obesogens may be playing a role.

In the current study, investigators exposed human and mouse mesenchymal stem cells (MSCs) and preadipocytes to triflumizole (TFZ), a fungicide widely used on food and ornamental crops. MSCs can differentiate into bone, cartilage, or fat cells; preadipocytes are precursor fat cells that mature into adipocytes in response to environmental cues. The investigators found that expression of obesity-related genes increased in treated cells from both species, and that lipid accumulation and expression of obesity-related genes increased in treated cells from both species.

The team then exposed three groups of pregnant mice to three different doses of TFZ and examined fat tissues and gene expression profiles of the offspring. Although exposed and unexposed offspring did not differ significantly in body weight, mice exposed to the lowest dose of TFZ prenatally showed increased mass of the "fat depot" (areas where fat is stored) compared with unexposed offspring. In contrast, fat depot mass did not differ from controls in animals treated with higher doses of TFZ. The lowest dose was 400 times lower than the established no-observed-adverse-effect level for TFZ exposure in rodents.

The authors observed that induced cultured MSCs from the exposed offspring appeared to be more likely to become fat cells than bone cells. TFZ has been identified as an activator of peroxisome proliferator-activated receptor gamma (PPARγ), which is known to regulate fat cell differentiation and gene expression. Treatment of exposed MSCs with a PPARγ blocker stopped their differentiation into fat cells, confirming that TFZ operates by this pathway.



As adipocytes fill with lipids from the diet and increase in number, fat mass grows.

Although the exposed offspring were of normal weight when they were sacrificed at 8 weeks, the authors suggest that changes in body weight might have increased with time, had the mice aged naturally. The increased fat mass in prenatally exposed mice was observed at exposure levels likely to be encountered by the general human population, according to the investigators (no actual data exist for human exposure to TFZ). They suggest that future studies should include biomonitoring of TFZ levels in humans and investigation of transgenerational effects and epigenetic mechanisms related to the chemical's potential influence on obesity.

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Exposure Intimacy

A New Metric for Assessing Chemical Intake

A new way to efficiently estimate human intake of a chemical based on its production and how it is used demonstrates that people's "exposure intimacy" with widely used chemicals varies dramatically [***EHP* 120(12):1678–1683; Nazaroff et al.**]. For example, the plasticizer bisphenol A (BPA) is one of the world's most heavily used chemicals, but its U.S. intake-to-production ratio (IPR) is over 100,000 times less than that of methyl paraben, a food preservative and antifungal agent. IPR estimates for human exposure to five commonly used phthalate plasticizers, the disinfectant *p*-dichlorobenzene, and the antibacterial agent triclosan fall in between these two extremes.

The IPR, reported as ppm, quantifies the fraction of the total amount of a chemical used in a country each year that gets into the country's population. The metric is calculated by dividing the population's estimated total intake of a chemical by the rate at which that chemical is produced or imported. So, for example, diethyl phthalate's rating of 7,700 ppm indicates that for every 1 million g of the chemical entering U.S. commerce, approximately 7,700 g is taken up by the aggregate population. The metric does not reflect the distribution of exposures within the population.

For this study, intake estimates for the nine chemicals assessed were based on urinary excretion data from the U.S. Centers for Disease Control and Prevention. The chemical manufacture and import data came from the U.S. Environmental Protection Agency's Chemical Data Reporting system.

The nine chemicals yielded a broad span of IPRs, which the researchers believe is a result of the variable opportunities for exposure associated with different chemical uses. For example, although the presence of BPA in the linings of food cans has a high potential for human exposure, its low IPR of 0.6 ppm likely reflects the fact that most BPA is used in polycarbonate plastics, where its potential for transfer to humans is relatively low. In contrast, methyl paraben's IPR of over 180,000 ppm is consistent with its presence in products with which people have close contact—foods, cosmetics, and pharmaceuticals.

The authors acknowledge that the limited availability of biomonitoring data currently hinders widespread use of the IPR. They nonetheless foresee that the metric could contribute to a framework for rapidly estimating human exposure to untested chemicals based on the chemicals' intended uses and anticipated production volumes.

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